

Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference M/44162-PCT	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/EP2004/006564	International filing date (day/month/year) 17.06.2004	Priority date (day/month/year) 18.06.2003
International Patent Classification (IPC) or national classification and IPC		
Applicant BASF AKTIENGESELLSCHAFT		

1.	This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2.	This REPORT consists of a total of 8 sheets, including this cover sheet.
3.	This report is also accompanied by ANNEXES, comprising: a. <input checked="" type="checkbox"/> (sent to the applicant and to the International Bureau) a total of 4 sheets, as follows: <input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions). <input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box. b. <input type="checkbox"/> (sent to the International Bureau only) a total of _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4.	This report contains indications relating to the following items: <input checked="" type="checkbox"/> Box No. I Basis of the report <input type="checkbox"/> Box No. II Priority <input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability <input type="checkbox"/> Box No. IV Lack of unity of invention <input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement <input type="checkbox"/> Box No. VI Certain documents cited <input type="checkbox"/> Box No. VII Certain defects in the international application <input type="checkbox"/> Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/EP	Authorized officer
Facsimile No.	Telephone No.

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Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This report is based on translations from the original language into the following language _____ which is the language of a translation furnished for the purposes of:
 - ☐ international search (Rule 12.3 and 23.1(b))
 - ☐ publication of the international application (Rule 12.4)
 - ☐ international preliminary examination (Rule 55.2 and/or 55.3)
2. With regard to the elements of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):
 - ☐ the international application as originally filed/furnished
 - ☒ the description:
 - pages 1-40 _____ as originally filed/furnished
 - pages* _____ received by this Authority on _____
 - pages* _____ received by this Authority on _____
 - ☒ the claims:
 - nos. _____ as originally filed/furnished
 - nos.* _____ as amended (together with any statement) under Article 19
 - nos.* 1-21 _____ received by this Authority on /filed with the demand
 - nos.* _____ received by this Authority on _____
 - ☐ the drawings:
 - sheets _____ as originally filed/furnished
 - sheets* _____ received by this Authority on _____
 - sheets* _____ received by this Authority on _____
 - ☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.
3. ☐ The amendments have resulted in the cancellation of:
 - ☐ the description, pages _____
 - ☐ the claims, nos. _____
 - ☐ the drawings, sheets/figs _____
 - ☐ the sequence listing (*specify*): _____
 - ☐ any table(s) related to sequence listing (*specify*): _____
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
 - ☐ the description, pages _____
 - ☐ the claims, nos. _____
 - ☐ the drawings, sheets/figs _____
 - ☐ the sequence listing (*specify*): _____
 - ☐ any table(s) related to sequence listing (*specify*): _____

* If item 4 applies, some or all of those sheets may be marked "superseded."

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-10, 12, 18-21	YES
	Claims	11, 13-17	NO
Inventive step (IS)	Claims	1-10, 12, 18-21	YES
	Claims	11, 13-17	NO
Industrial applicability (IA)	Claims	1-21	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

1. This report makes reference to the following documents:

D1: SILVIA M. GLÜCK ET AL.: "Lactate Racemase as a Versatile Tool for the Racemization of Alpha-Hydroxycarboxylic Acids" CHEMICKE LISTY, Vol. 97, No. 6, 1 June 2003 (2003-06-01), page 363, XP002301107, PRAHA, CZ - according to Prof. Vilim Simanek (co-editor of the Chemicke Listy), this document was made available to the public after the priority date, and is therefore not considered prior art under PCT Rule 64.2

D2: SCHNELL, BARBARA ET AL: "Enzymatic racemization and its application to synthetic biotransformations", ADVANCED SYNTHESIS & CATALYSIS, 345(6+7), pages 653-666, CODEN: ASCAF7; ISSN: 1615-4150, 13 June 2003 (2003-06-13), XP002301108

D3: LIU S-Q: "Practical implications of lactate and pyruvate metabolism by lactic acid bacteria in food and beverage fermentations." INTERNATIONAL JOURNAL OF FOOD MICROBIOLOGY, Vol. 83, No. 2, 15 June 2003 (2003-06-15), pages 115-131 ,

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	XP002301109, ISSN: 0168-1605
D4:	STRAUSS U T ET AL: "Deracemization of (+-)-mandelic acid using a lipase-mandelate racemase two-enzyme system" TETRAHEDRON ASYMMETRY 1999, UNITED KINGDOM, Vol. 10, No. 21 , 1999, pages 4079-4081, XP002301110, ISSN: 0957-4166
D5:	FELFER ULFRIED ET AL: "Substrate spectrum of mandelate racemase. Part 2. (Hetero)-aryl-substituted mandelate derivatives and modulation of activity", JOURNAL OF MOLECULAR CATALYSIS B ENZYMATIC, Vol. 15, No. 4-6, 1 November 2001 (2001-11-01), pages 213-222, XP002301111, ISSN: 1381-1177
D6:	SCHAFER SUSAN L ET AL: "Mechanism of the reaction catalyzed by mandelate racemase: Structure and mechanistic properties of the D270N mutant", BIOCHEMISTRY, Vol. 35, No. 18, 1996, pages 5662-5669, XP002301112, ISSN: 0006-2960
D7:	GARCIA-VILOCA M ET AL: "A QM/MM study of the racemization of vinylglycolate catalyzed by mandelate racemase enzyme", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, 31 JAN 2001 , Vol. 123, No. 4, 31 January 2001 (2001-01-31), pages 709-721, XP002301113, ISSN: 0002-7863
D8:	RONGSHI LI ET AL.: "Racemization of Vinylglycolate by Mandelates Racemase", JOURNAL OF ORGANIC CHEMISTRY, Vol. 60, No. 11, 1995, XP002301114
D9:	EP-A-0 596 466 (TANABE SEIYAKU CO), 11 May 1994 (1994-05-11)

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Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
2.	<u>Novelty and inventive step (PCT Article 33(2) and 33(3))</u>
2.1	<p>The subject matter of the present application is a process for isomerising alpha-hydroxycarboxylic acids using microbial lactate racemases with a broader activity spectrum, said lactate racemases <i>per se</i> and the nucleic acids that encode the same, screening methods for said racemases, expression vectors, recombinant micro-organisms which express the racemases, and processes for producing and isolating a protein with alpha-hydroxycarboxylic acid racemase activity.</p>
2.2	<p>The prior art, as disclosed in documents D2 to D9, describes racemisation processes of alpha-hydroxycarboxylic acids using enzymes or micro-organisms with high substrate specificity. Lactate racemases with a broader substrate spectrum, i.e. enzymes which racemise lactate and alpha-hydroxycarboxylic acids of general formula (I), and hence also their uses, are novel. Consequently, the present claims 1-10, 12 and 18-21 meet the requirements of PCT Article 33(2) for novelty.</p> <p>The enzymes <i>per se</i>, as well as the screening methods as per claims 8, 11 and 13-17, are not exclusively directed to lactate racemases with a broader substrate spectrum (i.e. with compounds of general formula (I)). The screening method as per claim 8 requires micro-organisms which express</p>

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	<p>alpha-hydroxycarboxylic acid-racemase activity and form or metabolise lactate, the latter activity not being necessarily linked to the racemase activity, i.e. enzymes with a narrow substrate spectrum are also screened. Already known enzymes and methods for isolating the same are thus covered by the claims, although claims 11-13 and 17 are not novel in the case of these subjects (see D6, Materials and Methods). As for the lactate racemases with a broader substrate spectrum, as mentioned in claim 1, they should be considered novel.</p> <p>2.3 Documents D2 to D6 can be regarded as the closest prior art. Those documents disclose racemisation processes using lactate or mandelate racemases with the known restrictions with regard to the substrates. Consequently, the present invention can be considered to address the technical problem of finding a biocatalyst suitable for isomerising alpha-hydroxycarboxylic acids, which do not belong to the substrate spectrum of mandelate racemase, which have a broader substrate spectrum in comparison with lactate racemase, and which can be used in corresponding isomerisation processes. The solution is the process as per claim 1, in which a lactate racemase (for example from the <u><i>Lactobacillus spp.</i></u> mutants as per claim 6) with a broader substrate spectrum is used. The prior art contains no indication of lactate racemase enzymes including compounds of general formula (I) with a broader substrate specificity, i.e. these subjects</p>

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can be considered to involve an inventive step in relation to the prior art. Since the screening methods and the enzymes *per se* are limited by the same restrictions, claims 1-10, 12 and 18-21 should be recognised to involve an inventive step.

2.4 Industrial applicability (PCT Article 33(4))

All the present claims meet the requirements of PCT Article 33(4) for industrial applicability.

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

BOX I

1. The claims 1-21 filed with the demand for international preliminary examination meet the requirements of PCT Article 34(2) and have therefore been used as the basis for the international preliminary examination.